IMPLEMENTATION OF CHROMATOGRAPHY DATA SYSTEM IN A QUALITY CONTROL LABORATORY IN THE PHARMACEUTICAL INDUSTRY

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Abstract: Chromatography is one of the main analytical techniques, especially in regulated analytical laboratories, where chromatographic analyses can comprise up to 80% of the total analytical workload. The Chromatography Data System is computer system with specialized software installed on it, which collects and analyzes chromatography results from instruments connected to the system. Today, when we operate with electronic records, the possibility of changing or copying the contents of electronic records, without leaving any visible trace of the change, is extremely high. To ensure the integrity of the data, the regulatory authorities require the computer systems validation in accordance with their requirements. The CDS systems are intended for use within regulated laboratories in pharmaceutical and related industries. The role of these systems in the R&D and QC is within Good Manufacturing Practice (GMP).

The implementation and validation of CDS systems is carried out to validate key functions of the system and later to bring the system to end users. Computerized Systems Validation is a process used to test, validate and formally document that a regulated computer-based system does exactly what it is designed to do in a consistent and accurate manner that is secure, reliable and traceable. This procedure is applied to GxP computerized system applications used at any point in the research, clinical testing, manufacturing, distribution and storage processes. Examples might include: Chromatography Data System (CDS), Laboratory Information Management System (LIMS), Laboratory Instrument Systems (LIS), Clinical Trial Monitoring Systems, PLC for Controlled Packaging Equipment Supervisory Control and Data Acquisition (SCADA), Distributed Control System (DCS), Enterprise Resource Planning (ERP) Systems, Manufacturing Execution System (MES), Batch Record System, Building Management Systems (BMS), Spreadsheets. In the pharmaceutical industry, the most widely used method is to follow the GAMP 5 guidelines and break the process down into its life cycle phases. As a basic starting point for identifying the process of validating a computerized system, V-model methodology approach to validation is used, which is the most widespread within the area of computer-based system validation in the pharmaceutical industry. In addition, there are a lot of supporting processes or activities that take place across the phases of the life cycle such as risk management, document management, repair activity, security management, etc and you should include them when visualizing the process.

Keywords: chromatography, CDS, validation, computer systems

1. INTRODUCTION

The first attempts to automate the analysis of chromatographic data electronically began in the early 70s of the last century. These analyzes used microprocessor-based integrators, special devices for measuring chromatographic peaks and processing calculations, and the results were printed on a printer/plotter that was directly connected to the system.

In 1980, with the development of personal computers, the first CDS (Chromatography Data System) project was developed in the form of computer software for Microsoft's Windows operating system. In the 90s of the last century with the advent of computers with higher performance, the use of CDS was implemented in networked systems, until the emergence of possibilities for remote control of instruments through method setting, acquisition and processing of data from analysis to transmission of the data in other data systems.

Today these functions have been refined and are used in liquid (LC) and gas chromatography (GC). In parallel, new innovations in liquid and gas chromatography instruments provide the potential for faster data acquisition, improved separation and high resolution of chromatograms.

Chromatography Data System is a computer system with installed specialized software, which collects and analyzes the chromatographic results obtained from the instruments connected to the system. The software packages used in CDS are mostly developed and provided by instrument manufacturers, and most of them provide a simple interface for obtaining and storing data. These packages have the ability to simulate chromatographic analysis, for the purpose of training, demonstration, method development or their optimization. (McDowall, 1999)

2. MATERIALS AND METHODS

The paper presents literary data, which are analyzed and compared with a real case of implementation and validation of a computerized system that is intended and used in quality control laboratories in the pharmaceutical industry.

3. DISCUSSIONS

Chromatography represents one of the main analytical techniques, especially in regulated analytical laboratories, where chromatographic analyzes occupy up to 80% of the total work tasks in the laboratory. The automation of the chromatographic analyzes (through the control of the instruments, obtaining data from them, integration and preparation of analysis reports) is carried out with the Chromatography Data System (CDS). Over time, the computer software used within CDS has been designed with a more systematic and structured approach, not only to improve the speed and efficiency of the chromatographic process, but also to ensure compliance with regulatory requirements (GxP). Now, these versions of computer software are created with a focus on the regulatory requirement to maintain data integrity. (McDowall & Burgess, 2015)

Although the CDS system provides an opportunity for a complete transition to electronic records, most of the laboratories still use a hybrid way of data storage (by printing reports on paper and manually signing them). This approach wastes the investment in CDS and increases the company's costs, by increasing the risk and complexity of the overall process.

Current Chromatography Data Systems (CDS) can be found in various shapes and sizes, and the choice of the laboratory will depend on the workload and available budget. There are three possible CDS configurations:

- standalone workstation (standalone iPC), which controls two or more chromatographs;
- standalone workstation (standalone iPC), which controls one chromatograph (LC-MS/GC-MS);
- a networked CDS system, which includes one or more central servers and has the ability to control several instruments, in one or more laboratories.

In a regulated environment, a CDS system should satisfy five main requirements of essential importance:

- CDS in a network environment,
- data management through a database,
- independent IT support,
- ability to connect with other instruments and systems,
- independent data file types, including metadata data. (McDowall & Burgess, 2015)

Data integrity

For regulated analyses, stand-alone workstations are not suitable and should not be used. These are foundations based on several facts (problem with resource management – impossibility of access to the system by different users at the same time; when processing data, the same workstation cannot be used to set up another analysis). There is also a single point of failure with this type of system, which is hard drive failure, risking the potential loss of regulated data.

From the perspective of compliance with regulatory requirements and the practical use of the CDS system, a network solution is the only option that regulated laboratories should consider. With a networked CDS system, even when using a single instrument, analysis can be performed on one workstation and data processing on another workstation in the office, since the data is available through a central server. In addition, the data located in the central servers are subject to regular backups, thus avoiding data loss.

To ensure the integrity, all data generated during the analysis must be stored securely, to prevent their deletion (intentionally or accidentally), as well as the possibility of tracking any changes made to the data by authorized personnel. That is why it is necessary for the CDS system to manage all data through a database. The main reasons for incorporating a database into the system are:

- management of all chromatographic data and associated contextual metadata data,
- ensuring safe and encrypted data storage,
- provision of data on the performed activities in the system (audit trail), which are independent of the data files,
- ability to monitor and manage chromatographic data effectively across analyses.

However, modern versions of CDS framework software use multiple database files organized in directories. This approach requires that files be protected from modification, copying or deletion by an unauthorized person. Also, access to modification of certain system settings of the operating system (e.g., system clock) must be restricted by authorized administrative personnel, i.e., ordinary users should not be able to access these parts of the system at all.

CDS as a regulatory requirement or good practice in analytical laboratories of the pharmaceutical industry

Chromatography Data Systems (CDS) are intended for use within regulated laboratories in the pharmaceutical and related industries. The role of these systems in research and development, and product quality control, within the framework of Good Manufacturing Practice (GMP), can be used to determine impurities in raw materials and

finished products, within the framework of process controls, analyzes for the examination of stability, etc. Regardless of its purpose within the regulated laboratory, it is necessary to validate the system in accordance with GMP requirements, as well as 21 CFR 11 (electronic records, rules for the use of electronic signatures). (McDowall, 2010)

Implementation and validation of CDS

Typically, most CDS systems implementation and validation projects last between 6 and 18 months to validate key system functions and then make the system available to end users. This means that in the worst-case scenario, by the time you complete the current system validation, the software manufacturer will probably release a new version, which you will have to implement and validate later. Because of the time and resources spent on this procedure, laboratories typically implement every second new version.

In an ideal case, implementation and validation should be carried out quickly and efficiently, so that the laboratory would prepare its user requirements specifications and request offers for the purchase of a certain system. The CDS project requires a multidisciplinary approach, involving people from the laboratory, the IT department and the Quality Assurance (QA) department. The project team should be trained and have access to the system from the very beginning of implementation, in order to understand the functions of the system, as well as its configurability (possibility of own calculations and reports). This way the user requirements will be implemented to fit the purchased CDS system, which will be different from the generic delivered system. The risk management analysis will focus on certain functions within the system that should be tested as part of the validation process. Final system configurations such as master data entry and report templates should be performed after the validation process is completed.

In validating computer systems, pharmaceutical practice uses a classic V-model approach.

Computerized System Life Cycle

The life cycle of computerized systems is made up of activities that start from the initial concept of the system, until the cessation of operation of the system (retirement).

The life cycle of a computerized system contains four main stages:

- concept,
- designing,
- using the system and
- cessation of operation of the computerized system.

Validation of computerized systems takes place in the design phase. This phase includes several stages:

- planning,
- specification, configuration and development,
- verification and
- preparing reports and putting the system into production. (Rusjan, 2020)

The planning sub-process begins with the need for a new system. The potential user of the new computerized system creates user requirements, better known as User Requirement Specification (URS). Each request has its own unique code (e.g. URS-01, etc.), all in order to ensure the traceability of those requests in the following steps of system validation and prevention of forgetting a certain required system configuration. Encrypting user requests also provides control over testing system functionality. Of course, not only users are involved in the development of user requirements, but also experts from Quality Assurance and experts in the field of computerized systems. These persons add additional user requirements related to data integrity (eg prevention of data deletion, restrictions on data access for different users, recording of all events in an audit trail, etc.). The following table shows an example of several user requests related to a CDS system.

After defining user requirements and choosing a computerized system (hardware and software), it is classified according to the GAMP categorization, which is a standard for computerized systems in the pharmaceutical industry. This categorization is done on the basis of a system risk assessment (High Level Risk Assessment – HLRA).

The computerized system validation process continues with the creation of a system validation plan (VP). The validation plan is a document that covers the methods and principles of validation of the computerized system. The basis for creating this document is the user requirements and the risk assessment, which were previously prepared and approved by the system implementation and validation team. The validation plan explains all the activities that are planned and should be performed to make a successful system validation, as well as which documents (SOPs, work instructions) should be prepared before putting the system into production and the trainings that should be to be implemented to the users of the system. Also, this document indicates which documents will be created during the system validation process. The validation plan also specifies who will write, check and approve these documents.

The user requirements (URS) represent the basis for the creation of further documents that describe the design and functionalities of the system. This includes the Functional Specification (FS), the Hardware Design Specification (HDS) and the Software Design Specification (SDS). This documentation is usually prepared by the company - supplier of the computerized system and it explains the design and functionalities of the system in relation to user requirements.

When reviewing the functional specification of the system (FS), all differences in terms of user requirements and the entire process are formalized in one document called Design Qualification (DQ).

After the preparation, verification and approval of the documents that describe the design and functionalities of the system (FS, HDS and SDS) in correlation with the user requirements, a document is prepared that performs a risk assessment of the functionalities of the system (Functional Risk Assessment – FRA). The FRA document evaluates each user request, according to the criticality of each system functionality. An assessment is made of the possible risks that may occur during the failure or non-fulfillment of each functionality, their frequency of occurrence, the criticality of these events, in terms of the impact on product quality, patient safety and evaluation of the possibility of detecting an incorrect function or error. Based on these results from the assessment of each functionality's criticality, a decision is made as to what type of testing will be selected for each functionality separately. Where the risk of system malfunction is high, installation qualification (IQ), operational qualification (OQ) and system performance qualification (PQ) should be carried out as appropriate during the verification phase. (European Compliance Academy, 2011a)

As part of the verification phase, testing should be carried out, in order to confirm that the computerized system is working according to the user requirements, this is checked and confirmed through IQ, OQ and PQ tests. First, the planning of these tests is carried out, in accordance with the validation plan. Then the test documentation is prepared, which states the test specifications, which functionalities would be tested and what is the expected result of the testing.

Testing is carried out in accordance with a pre-prepared test plan, on pre-approved test specifications that are properly prepared for each test (IQ, OQ and PQ), and are correlated with the results of the risk assessment of system functionalities (FRA).

During the installation of the computerized system, installation qualification (IQ) tests are performed, which is a documented verification that the installation has been carried out in accordance with the previously approved specifications.

Operational Qualification (OQ) tests represent documented verification of pre-approved specifications that a computerized system performs all intended operations for which it is intended, within expected operating limits.

System Performance Qualification (PQ) tests verify that the computerized system has the capacity to perform all operations in a production environment in accordance with the specification.

The results of these tests, which are documented during the tests, are test reports. In cases where a testing error occurred or the test was not successful or partially successful, this is recorded as a test deviation. In cases where a deviation appears, where it is necessary to make a correction to the design of the computerized system, retesting is carried out. Once it has been confirmed by retesting that the system is operating within specifications, the deviation is considered resolved. All testing and deviations are summarized in the Test and Deviation Report document.

All user requirements that are defined and sent to the computerized system supplier and then processed in the functional system specification (FS), hardware design specification (HDS) and software design specification (SDS), which are tested and documented in the IQ, OQ and PQ tests are summarized in one document called the Traceability Matrix (TM). In this document, each user request is connected according to the code with each item of the system functionality specification and with which test it is confirmed that that item really works according to the required parameters.

When all activities are completed, a validation report (Validation Report – VR) is prepared. This report presents a brief overview of the activities undertaken during the verification of the functionalities of the computerized system. The conclusion of this document should state the status of the computerized system or that it has been validated. Most often, the last signature of the approval of the report indicates the system validation date (CSV date).

In certain cases, a Release to production document can be prepared, with which the members of the validation team, the process owner and the system owner confirm that the computerized system is ready to be released into production. (European Compliance Academy, 2011b)

Final preparations before release to production environment

It is of particular importance that before the introduction of the system into operation, the end users in the laboratory should be adequately trained in the use of the system. Users of the new CDS system would be less productive until they fully familiarize themselves with the new system's functionalities, compared to the old software they were

using. Since the process of implementation and validation requires a large part of laboratory resources, the inclusion of instruments within the framework of the CDS system should be in several stages.

Further work within the CDS system is ensured and controlled through written procedures. Therefore, during system validation, it is necessary to write and implement standard operating procedures (SOPs) and work instructions, which will be available to the staff in their daily work, and will be training material for newly employed users.

Implementation and validation example of Chromatography data system

In a pharmaceutical industry, a CDS system has been implemented that unites the liquid and gas chromatographic systems used in the laboratories of Quality Control and Research and Development.

The beginning of the project dates back to the beginning of 2017, where a decision was made to purchase a system and form a project team for the implementation and validation of the system, composed of people from the Quality Control, Research and Development, IT department and Quality Assurance departments.

The system was put into operation in January 2018, with some of the instruments being migrated to CDS. Furthermore, with the gradual migration of the instruments and the inclusion of new instruments within the Chromatography Data System in several stages, the rest of the instruments were also connected.

4. CONCLUSIONS

The need for Chromatography Data System implementation within a regulated laboratory is inevitable, due to regulatory requirements (GxP) with a focus on the regulatory requirement to maintain data integrity.

The process of implementation and validation is long-term and requires a large number of resources (personnel and instruments). The literature says that the ideal period for system validation is 3 months, but in practice this takes longer.

However, after the successful implementation of the CDS system, the benefits of using it include faster and more efficient analysis, as well as avoiding errors during data transmission. The system complies with the regulatory requirements, such as the data on the activities performed in the system (audit trail), the controlled access of the end users and the creation of backup copies and the recovery of data from them (backup and restore).

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